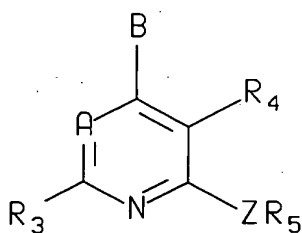
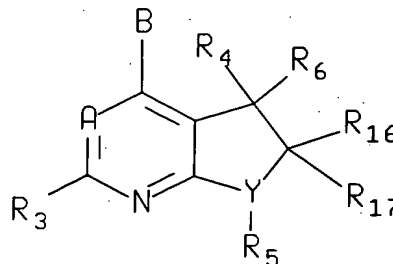


Abstract

Corticotropin-releasing factor (CRF) antagonists having the formulae

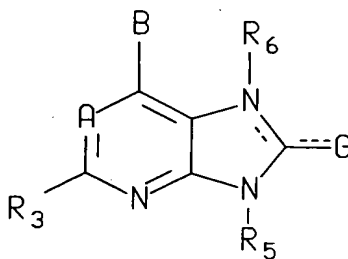


I



II

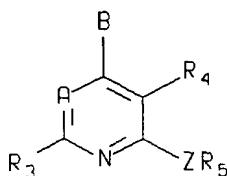
or



III

- 5 wherein the dashed lines, A, B, Y, Z, G, R₃, R₄, R₅, R₆, R₁₆ and R₁₇ are as defined in the application, and processes for preparing them. These compounds and their pharmaceutically acceptable salts are useful in the treatment disorders including CNS and stress-related disorders.

1. A compound of the formula



I

or a pharmaceutically acceptable salt thereof, wherein

A is -CR₇;

B is -NR₁R₂, -CR₁R₂R₁₁, -C(=CR₂R₁₂)R₁, -NHCHR₁R₂, -OCHR₁R₂, -SCHR₁R₂, -CHR₂OR₁, -CHR₁OR₂, -CHR₂SR₁, -C(S)R₂, -C(O)R₂, -CHR₂NR₁R₂, -CHR₁NHR₂, -CHR₁N(CH₃)R₂, or -NR₁₂NR₁R₂;

Z is NH, O, S, -N(C₁-C₂ alkyl), -NC(O)CF₃, or -C(R₁₃R₁₄), wherein R₁₃ and R₁₄ are each, independently, hydrogen, trifluoromethyl or methyl, or one of R₁₃ and R₁₄ is cyano and the other is hydrogen or methyl, or -C(R₁₃R₁₄) is a cyclopropyl group, or Z is nitrogen or CH and forms a five or six membered heterocyclic ring fused with R₅, which ring optionally includes two or three further hetero members selected independently from oxygen, nitrogen, NR₁₂, and S(O)_m, and optionally includes from one to three double bonds, and is optionally substituted with halo, C₁-C₄ alkyl, -O(C₁-C₄ alkyl), NH₂, NHCH₃, N(CH₃)₂, CF₃, or OCF₃, with the proviso that said ring does not include any -S-S-, -S-O-, -N-S-, or -O-O- bonds, and does not include more than two oxygen or S(O)_m heterologous members;

R₁ is C(O)H, C(O)(C₁-C₆ alkyl), C(O)(C₁-C₆ alkylene)(C₃-C₈ cycloalkyl), C(O)(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), C(O)(C₁-C₆ alkylene)(C₄-C₈ heterocycloalkyl), -C(O)(C₃-C₈ cycloalkylene)(C₄-C₈ heterocycloalkyl), C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₄-C₈ heterocycloalkyl, -(C₁-C₆ alkylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), -(C₁-C₆ alkylene)(C₄-C₈ heterocycloalkyl), -(C₃-C₈ cycloalkylene)(C₄-C₈ heterocycloalkyl), or -O-aryl, or -O-(C₁-C₆ alkylene)-aryl; wherein said aryl, C₄-C₈ heterocycloalkyl, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkylene, and C₁-C₆ alkylene groups may each independently be optionally substituted with from one to six fluoro and may each independently be optionally substituted with one or two substituents R₈ independently selected from the group consisting of C₁-C₄ alkyl, -C₃-C₈ cycloalkyl, hydroxy, chloro, bromo, iodo, CF₃, -O-(C₁-C₆ alkyl), -O-(C₃-C₅ cycloalkyl), -O-CO-(C₁-C₄ alkyl), -O-CO-NH(C₁-C₄ alkyl), -O-CO-N(R₂₄)(R₂₅), -N(R₂₄)(R₂₅), -S(C₁-C₄ alkyl), -S(C₃-C₅ cycloalkyl), -N(C₁-C₄alkyl)CO(C₁-C₄ alkyl), -NHCO(C₁-C₄ alkyl), -COO(C₁-C₄ alkyl), -CONH(C₁-C₄ alkyl), -CON(C₁-C₄ alkyl)(C₁-C₂ alkyl), CN, NO₂, -OSO₂(C₁-C₄ alkyl), S⁺(C₁-C₆ alkyl)(C₁-C₂ alkyl)I⁻, -SO(C₁-C₄ alkyl) and -SO₂(C₁-C₄ alkyl); and wherein the C₁-C₆ alkyl, C₁-C₆ alkylene, C₅-C₈ cycloalkyl, C₅-C₈ cycloalkylene, and C₅-C₈ heterocycloalkyl moieties of R₁ may optionally independently include from one to three double or triple bonds; and wherein the C₁-C₄ alkyl moieties and C₁-C₆ alkyl moieties of R₈ can optionally

independently be substituted with hydroxy, amino, C₁-C₄ alkyl, aryl, -CH₂-aryl, C₃-C₅ cycloalkyl, or -O-(C₁-C₄ alkyl), and can optionally independently be substituted with from one to six fluoro, and can optionally include one or two double or triple bonds; and wherein each heterocycloalkyl group of R₁ includes from one to three heteromoieties selected from oxygen, S(O)_m, nitrogen, and NR₁₂;

R₂ is hydrogen, C₁-C₁₂ alkyl, C₃-C₈ cycloalkyl, C₄-C₈ heterocycloalkyl, -(C₁-C₆ alkylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), -(C₁-C₆ alkylene)(C₄-C₈ heterocycloalkyl), -(C₃-C₈ cycloalkylene)(C₄-C₈ heterocycloalkyl), aryl, -(C₁-C₆ alkylene)aryl, or -(C₃-C₈ cycloalkylene)(aryl); wherein each of the foregoing R₂ groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro, and C₁-C₆ alkyl, wherein one of said one to three substituents can further be selected from bromo, iodo, C₁-C₆ alkoxy, -OH, -O-CO-(C₁-C₆ alkyl), -O-CO-N(C₁-C₄ alkyl)(C₁-C₂ alkyl), -S(C₁-C₆ alkyl), -S(O)(C₁-C₆ alkyl), -S(O)₂(C₁-C₆ alkyl), S⁺(C₁-C₆ alkyl)(C₁-C₂ alkyl)I⁻, CN, and NO₂; and wherein the C₁-C₁₂ alkyl, -(C₁-C₆ alkylene), -(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene), and -(C₄-C₈ heterocycloalkyl) moieties of R₂ may optionally independently include from one to three double or triple bonds; and wherein each heterocycloalkyl group of R₂ includes from one to three heteromoieties selected from oxygen, S(O)_m, nitrogen, and NR₁₂;

or when R₁ and R₂ are as in -NHCHR₁R₂, -OCHR₁R₂, -SCHR₁R₂, -CHR₁R₂ or -NR₁R₂, R₁ and R₂ of B may form a saturated 5- to 8-membered ring which may optionally include one or two double bonds and in which one or two of the ring carbons may optionally be replaced by an oxygen, S(O)_m, nitrogen or NR₁₂; and which ring can optionally be substituted with from 1 to 3 substituents selected from the group consisting of hydroxy, C₁-C₄ alkyl, fluoro, chloro, bromo, iodo, CF₃, -O-(C₁-C₄ alkyl), -O-CO-(C₁-C₄ alkyl), -O-CO-NH(C₁-C₄ alkyl), -O-CO-N(C₁-C₄ alkyl)(C₁-C₂ alkyl), -NH(C₁-C₄ alkyl), -N(C₁-C₂ alkyl)(C₁-C₄ alkyl), -S(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)CO(C₁-C₄ alkyl), -NHCO(C₁-C₄ alkyl), -COO(C₁-C₄ alkyl), -CONH(C₁-C₄ alkyl), -CON(C₁-C₄ alkyl)(C₁-C₂ alkyl), CN, NO₂, -OSO₂(C₁-C₄ alkyl), -SO(C₁-C₄ alkyl), and -SO₂(C₁-C₄ alkyl), wherein one of said one to three substituents can further be selected from phenyl;

R₃ is methyl, ethyl, fluoro, chloro, bromo, iodo, cyano, methoxy, OCF₃, NH₂, NH(C₁-C₂ alkyl), N(CH₃)₂, -NHCOCF₃, -NHCH₂CF₃, S(O)_m(C₁-C₄ alkyl), CONH₂, -CONHCH₃, CON(CH₃)₂, -CF₃, or CH₂OCH₃;

R₄ is hydrogen, C₁-C₄ alkyl, C₃-C₅ cycloalkyl, -(C₁-C₄ alkylene)(C₃-C₅ cycloalkyl), -(C₃-C₅ cycloalkylene)(C₃-C₅ cycloalkyl), cyano, fluoro, chloro, bromo, iodo, -OR₂₄, C₁-C₆ alkoxy, -O-(C₃-C₅ cycloalkyl), -O-(C₁-C₄ alkylene)(C₃-C₅ cycloalkyl), -O-(C₃-C₅ cycloalkylene)(C₃-C₅ cycloalkyl), -CH₂SC(S)O(C₁-C₄ alkyl), -CH₂OCF₃, CF₃, amino, nitro, -NR₂₄R₂₅, -(C₁-C₄ alkylene)-OR₂₄, -(C₁-C₄ alkylene)Cl, -(C₁-C₄ alkylene)NR₂₄R₂₅, -NHCOR₂₄, -NHCONR₂₄R₂₅, -C=NOR₂₄, -NHNOR₂₄R₂₅, -S(O)_mR₂₄, -C(O)R₂₄, -OC(O)R₂₄, -C(O)CN, -C(O)NR₂₄R₂₅, -C(O)NHNOR₂₄R₂₅, and -COOR₂₄, wherein the alkyl and alkylene groups of R₄ may optionally independently include one or two double or triple bonds and may optionally independently be substituted with one or two substituents R₁₀

independently selected from hydroxy, amino, -NHCOCH_3 , $\text{-NHCOCH}_2\text{Cl}$, $\text{-NH(C}_1\text{-C}_2\text{ alkyl)}$, $\text{-N(C}_1\text{-C}_2\text{ alkyl)(C}_1\text{-C}_2\text{ alkyl)}$, $\text{-COO(C}_1\text{-C}_4\text{ alkyl)}$, -COOH , $\text{-CO(C}_1\text{-C}_4\text{ alkyl)}$, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_1\text{-C}_3$ thioalkyl, cyano and nitro, and with one to four substituents independently selected from fluoro and chloro;

R_5 is aryl or heteroaryl and is substituted with from one to four substituents R_{27} independently selected from halo, $\text{C}_1\text{-C}_{10}$ alkyl, $\text{-(C}_1\text{-C}_4\text{ alkylene)(C}_3\text{-C}_8\text{ cycloalkyl)}$, $\text{-(C}_1\text{-C}_4\text{ alkylene)(C}_4\text{-C}_8\text{ heterocycloalkyl)}$, $\text{-(C}_3\text{-C}_8\text{ cycloalkyl)}$, $\text{-(C}_4\text{-C}_8\text{ heterocycloalkyl)}$, $\text{-(C}_3\text{-C}_8\text{ cycloalkylene)(C}_3\text{-C}_8\text{ cycloalkyl)}$, $\text{-(C}_3\text{-C}_8\text{ cycloalkylene)(C}_4\text{-C}_8\text{ heterocycloalkyl)}$, $\text{C}_1\text{-C}_4$ haloalkyl, $\text{C}_1\text{-C}_4$ haloalkoxy, nitro, cyano, $\text{-NR}_{24}\text{R}_{25}$, $\text{-NR}_{24}\text{COR}_{25}$, $\text{-NR}_{24}\text{CO}_2\text{R}_{26}$, -COR_{24} , -OR_{25} , $\text{-CONR}_{24}\text{R}_{25}$, $\text{-CO(NOR}_{22})\text{R}_{23}$, $\text{-CO}_2\text{R}_{26}$, $\text{-C=N(OR}_{22})\text{R}_{23}$, and $\text{-S(O)}_m\text{R}_{23}$; wherein said $\text{C}_1\text{-C}_{10}$ alkyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{(C}_1\text{-C}_4\text{ alkylene)}$, $\text{(C}_3\text{-C}_8\text{ cycloalkyl)}$, $\text{(C}_3\text{-C}_8\text{ cycloalkylene)}$, and $\text{(C}_4\text{-C}_8\text{ heterocycloalkyl)}$ groups can be optionally substituted with from one to three substituents independently selected from $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{(C}_1\text{-C}_4\text{ alkylene)(C}_3\text{-C}_8\text{ cycloalkyl)}$, $\text{-(C}_3\text{-C}_8\text{ cycloalkylene)(C}_3\text{-C}_8\text{ cycloalkyl)}$, $\text{C}_1\text{-C}_4$ haloalkyl, hydroxy, $\text{C}_1\text{-C}_6$ alkoxy, nitro halo, cyano, $\text{-NR}_{24}\text{R}_{25}$, $\text{-NR}_{24}\text{COR}_{25}$, $\text{NR}_{24}\text{CO}_2\text{R}_{26}$, -COR_{24} , -OR_{25} , $\text{-CONR}_{24}\text{R}_{25}$, CO_2R_{26} , $\text{-CO(NOR}_{22})\text{R}_{25}$, and $\text{-S(O)}_m\text{R}_{23}$; and wherein two adjacent substituents of the R_5 group can optionally form a 5-7 membered ring, saturated or unsaturated, fused to R^5 , which ring optionally can include one, two, or three heterologous members independently selected from O, S(O)_m , and N, but not any -S-S- , -O-O- , -S-O- , or -N-S- bonds, and which ring is optionally substituted with $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{-(C}_1\text{-C}_4\text{ alkylene)(C}_3\text{-C}_8\text{ cycloalkyl)}$, $\text{-(C}_3\text{-C}_8\text{ cycloalkylene)(C}_3\text{-C}_8\text{ cycloalkyl)}$, $\text{C}_1\text{-C}_4$ haloalkyl, nitro, halo, cyano $\text{-NR}_{24}\text{R}_{25}$, $\text{NR}_{24}\text{COR}_{25}$, $\text{NR}_{24}\text{CO}_2\text{R}_{26}$, -COR_{24} , -OR_{25} , $\text{-CONR}_{24}\text{R}_{25}$, CO_2R_{26} , $\text{-CO(NOR}_{26})\text{R}_{25}$, or $\text{-S(O)}_m\text{R}_{23}$; wherein one of said one to four optional substituents R_{27} can further be selected from $\text{-SO}_2\text{NH(C}_1\text{-C}_4\text{ alkyl)}$, $\text{-SO}_2\text{NH(C}_1\text{-C}_4\text{ alkylene)(C}_3\text{-C}_8\text{ cycloalkyl)}$, $\text{-SO}_2\text{NH(C}_3\text{-C}_8\text{ cycloalkyl)}$, $\text{-SO}_2\text{NH(C}_3\text{-C}_8\text{ cycloalkylene)(C}_3\text{-C}_8\text{ cycloalkyl)}$, $\text{-SO}_2\text{N(C}_1\text{-C}_4\text{ alkyl)(C}_1\text{-C}_2\text{ alkyl)}$, $\text{-SO}_2\text{NH}_2$, $\text{-NHSO}_2\text{(C}_1\text{-C}_4\text{ alkyl)}$, $\text{-NHSO}_2\text{(C}_3\text{-C}_8\text{ cycloalkyl)}$, $\text{-NHSO}_2\text{(C}_1\text{-C}_4\text{ alkylene)(C}_3\text{-C}_8\text{ cycloalkyl)}$, and $\text{-NHSO}_2\text{(C}_3\text{-C}_8\text{ cycloalkylene)(C}_3\text{-C}_8\text{ cycloalkyl)}$; and wherein the alkyl, and alkylene groups of R_5 may independently optionally include one double or triple bond;

R_6 is hydrogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{-(C}_1\text{-C}_6\text{ alkylene)(C}_3\text{-C}_8\text{ cycloalkyl)}$, or $\text{-(C}_3\text{-C}_8\text{ cycloalkylene)(C}_3\text{-C}_8\text{ cycloalkyl)}$, wherein said alkyl and cycloalkyl may optionally be substituted with one hydroxy, methoxy, ethoxy or fluoro group;

R_7 is hydrogen, methyl, fluoro, chloro, bromo, iodo, cyano, hydroxy, $\text{-O(C}_1\text{-C}_2\text{ alkyl)}$, -O(cyclopropyl) , $\text{-COO(C}_1\text{-C}_2\text{ alkyl)}$, $\text{-COO(C}_3\text{-C}_8\text{ cycloalkyl)}$, -OCF_3 , CF_3 , $\text{-CH}_2\text{OH}$, or CH_2OCH_3 ;

R_{11} is hydrogen, hydroxy, fluoro, ethoxy, or methoxy;

R_{12} is hydrogen or $\text{C}_1\text{-C}_4$ alkyl;

R_{22} is independently at each occurrence selected from hydrogen, $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_1\text{-C}_4$ haloalkyl, $\text{C}_3\text{-C}_6$ alkenyl, $\text{C}_3\text{-C}_6$ alkynyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{(C}_3\text{-C}_8\text{ cycloalkylene)(C}_3\text{-C}_8\text{ cycloalkyl)}$, and $\text{(C}_1\text{-C}_4\text{ alkylene)(C}_3\text{-C}_8\text{ cycloalkyl)}$;

R_{23} is independently at each occurrence selected from $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_1\text{-C}_4$ haloalkyl, $\text{C}_2\text{-C}_8$

alkoxyalkyl, C₃-C₈ cycloalkyl, -(C₁-C₄ alkylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), aryl, -(C₁-C₄ alkylene)aryl, piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine, and thiomorpholine;

R₂₄ and R₂₅ are independently at each occurrence selected from hydrogen, -C₁-C₄ alkyl, C₁-C₄ haloalkyl, especially CF₃, -CHF₂, CF₂CF₃, or CH₂CF₃, -(C₁-C₄ alkylene)OH, -(C₁-C₄ alkylene)-O-(C₁-C₄ alkyl), -(C₁-C₄ alkylene)-O-(C₃-C₅ cycloalkyl), C₃-C₈ cycloalkyl, -(C₁-C₄ alkylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), -C₄-C₈ heterocycloalkyl, -(C₁-C₄ alkylene)(C₄-C₈ heterocycloalkyl), -(C₃-C₈ cycloalkylene)(C₄-C₈ heterocycloalkyl), aryl, and -(C₁-C₄ alkylene)(aryl), wherein the -C₄-C₈ heterocycloalkyl groups can each independently optionally be substituted with aryl, CH₂-aryl, or C₁-C₄ alkyl, and can optionally include one or two double or triple bonds; or, when R₂₄ and R₂₅ are as NR₂₄R₂₅, -C(O)NR₂₄R₂₅, -(C₁-C₄ alkylene)NR₂₄R₂₅, or -NHCONR₂₄R₂₅, then NR₂₄R₂₅ may further optionally form a 4 to 8 membered heterocyclic ring optionally including one or two further hetero members independently selected from S(O)_m, oxygen, nitrogen, and NR₁₂, and optionally including from one to three double bonds;

R₂₆ is independently at each occurrence selected from C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₃-C₈ cycloalkyl, -(C₁-C₄ alkylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), aryl, and -(C₁-C₄ alkylene)(aryl); and

wherein each m is independently zero, one, or two,

with the proviso that heterocycloalkyl groups of the compound of formula I do not include any -S-S-, -S-O-, -N-S-, or -O-O- bonds, and do not include more than two oxygen or S(O)_m heterologous members.

2. A compound according to claim 1, wherein R₄ is -NHCH₂CF₃, -CONHNNH₂, -CONHNNHCH₃, -OCF₃, fluoro, -OCHF₂, -OCH₂(C₃-C₅ cycloalkyl), -O-(C₃-C₅ cycloalkyl), -SCH₂(C₃-C₅ cycloalkyl), -S(C₃-C₅ cycloalkyl), -OCH₃, -CH₃, -CH₂CH₃, chloro, bromo, -CF₃, -CH₂OH, -CH₂OCH₃, -CH₂OCF₃, -SCH₃, -S(O)CH₃, -S(O)₂CH₃, -C(O)CH₃, -NR₂₄R₂₅, -NO₂, -CH(OH)CH₃, or -CN.

3. A compound according to claim 1, wherein R₄ is -C(O)NR₂₄R₂₅ or -C(O)NHNHR₂₄R₂₅.

4. A compound according to claim 1, wherein R₄ is -(C₁-C₄ alkylene)NR₂₄R₂₅.

5. A compound according to claim 1, wherein R₄ is -COOCH₃ or -COOCH₂CH₃.

6. A compound of formula I according to claim 1, wherein Z is O; B is -NHCHR₁R₂, wherein R₁ is -C(O)H, -C(O)(C₁-C₆ alkyl), or -C₁-C₆ alkyl, wherein said C₁-C₆ alkyl is optionally substituted with from one to six fluoro atoms or one or two R₈ independently selected from -C₁-C₄ alkyl, hydroxy and -O-(C₁-C₆ alkyl), and wherein R₂ is -C₁-C₁₂ alkyl optionally including from one to three double or triple bonds and optionally substituted with from one three substituents selected from fluoro and C₁-C₆ alkyl; R₅ is phenyl, pyridyl or pyrimidyl, substituted with two or

three R₂₇ groups selected from halo, -(C₁-C₄ haloalkyl), -C(O)R₂₄, -OR₂₅, -C(O)NR₂₄R₂₅, and C₁-C₁₀ alkyl which is optionally substituted with one to three substituents selected from hydroxy, C₁-C₆ alkoxy, and -NR₂₄R₂₅; and R₄ is -C(O)NR₂₄R₂₅.

7. A compound of formula I according to claim 1, wherein Z is O; B is -NHCHR₁R₂, wherein R₁ of -NHCHR₁R₂ is -C(O)H, -C(O)(C₁-C₆ alkyl), or -C₁-C₆ alkyl, wherein said C₁-C₆ alkyl is optionally substituted with from one to six fluoro atoms or one or two R₈ independently selected from -C₁-C₄ alkyl, hydroxy and -O-(C₁-C₆ alkyl), and wherein R₂ of -NHCHR₁R₂ is -C₁-C₁₂ alkyl optionally including from one to three double or triple bonds and optionally substituted with from one three substituents selected from fluoro and C₁-C₆ alkyl; R₅ is phenyl, pyridyl or pyrimidyl, substituted with two or three R₂₇ groups selected from halo, -(C₁-C₄ haloalkyl), -C(O)R₂₄, -OR₂₅, -C(O)NR₂₄R₂₅, and C₁-C₁₀ alkyl which is optionally substituted with one to three substituents selected from hydroxy, C₁-C₆ alkoxy, and -NR₂₄R₂₅; and R₄ is -NR₁R₂, wherein R₁ of -NR₁R₂ is C₁-C₆ alkyl, C₃-C₈ cycloalkyl, or -(C₁-C₆ alkylene)(C₃-C₈ cycloalkyl), and R₂ of -NR₁R₂ is C₁-C₁₂ alkyl optionally including from one to three double or triple bonds and optionally substituted with from one three fluoro atoms.

8. A compound according to claim 1 selected from:

2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-hydroxymethyl-propylamino)-6,N-dimethyl-nicotinamide;

2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-methoxymethyl-propylamino)-6,N-dimethyl-nicotinamide;

2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-methoxymethyl-propylamino)-6-methyl-nicotinamide;

2-(4-bromo-2-methoxy-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-nicotinamide;

2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-ethyl-2-methoxy-propylamino)-6-methyl-nicotinamide;

2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-ethyl-2-methoxy-propylamino)-6,N-dimethyl-nicotinamide;

2-(4-chloro-2-trifluoromethoxy-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-nicotinamide;

2-(4-chloro-2-trifluoromethoxy-phenoxy)-4-(1-ethyl-propylamino)-6-N-dimethyl-nicotinamide;

2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1S,2R-1-ethyl-2-methoxy-propylamino)-6,N-dimethyl-nicotinamide;

2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1S,2S-1-ethyl-2-methoxy-propylamino)-6,N-dimethyl-nicotinamide;

2-(4-bromo-2-methoxy-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-nicotinonitrile;

4-[4-(1-ethyl-propoxy)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethyl-benzamide;

2-(4-chloro-2,6-dimethyl-phenoxy)-6-methyl-4-(1-methylsulfanylmethyl-propylamino)-nicotinic acid methyl ester;

2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-hydroxymethyl-propylamino)-6-methyl-nicotinic acid methyl ester;

2-(4-bromo-2,6-dimethyl-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-nicotinonitrile;

2-(4-chloro-2-trifluoromethoxy-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-nicotinic acid methyl ester; and

2-(4-chloro-2,6-dimethyl-phenoxy)-6-methyl-4-(tetrahydro-furan-3-ylamino)-nicotinic acid methyl ester;

and pharmaceutically acceptable salts thereof.

9. A pharmaceutical composition for the treatment of (a) a disorder or condition the treatment of which can be effected or facilitated by antagonizing CRF, or (b) a disorder or condition selected from inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic; phobias, including social phobia, agoraphobia, and specific phobias; obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders such as depression, including major depression, single episode depression, recurrent depression, child abuse induced depression, mood disorders associated with premenstrual syndrome, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; chronic fatigue syndrome; stress-induced headache; irritable bowel syndrome; spastic colon; post operative ileus; ulcer; diarrhea; stress-induced fever; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases; hemorrhagic stress; chemical dependencies or addictions, including dependencies or addictions to alcohol, cocaine, heroin, benzodiazapines, or other drugs; drug or alcohol withdrawal symptoms; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiuretic hormone; head trauma; spinal cord trauma; ischemic neuronal damage, including cerebral ischemia, for example cerebral hippocampal ischemia; excitotoxic neuronal damage; epilepsy; stroke; immune dysfunctions including stress induced immune dysfunctions, including porcine stress syndrome, bovine shipping fever, equine paroxysmal fibrillation, confinement dysfunction in chicken, sheering stress in sheep, and human-animal interaction stress in dogs; muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; hypertension; tachycardia; congestive heart failure; osteoporosis and premature birth in a mammal or bird, comprising an amount of a compound according to claim 1 that is effective in the treatment of such disorder or condition, and a pharmaceutically acceptable carrier.

10. A method for the treatment of (a) a disorder or condition the treatment of which can be effected or facilitated by antagonizing CRF, or (b) a disorder or condition selected from

inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic; phobias, including social phobia, agoraphobia, and specific phobias; obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders such as depression, including major depression, single episode depression, recurrent depression, child abuse induced depression, mood disorders associated with premenstrual syndrome, and postpartum depression; dysthymia; bipolar disorders; cyclothymia; chronic fatigue syndrome; stress-induced headache; irritable bowel syndrome spastic colon; post operative ileus; ulcer; diarrhea; stress-induced fever; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases; hemorrhagic stress; chemical dependencies or addictions, including dependencies or addictions to alcohol, cocaine, heroin, benzodiazapines, or other drugs; drug or alcohol withdrawal symptoms; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiuretic hormone; head trauma; spinal cord trauma; ischemic neuronal damage, including cerebral ischemia, for example cerebral hippocampal ischemia; excitotoxic neuronal damage; epilepsy; stroke; immune dysfunctions including stress induced immune dysfunctions, including porcine stress syndrome, bovine shipping fever, equine paroxysmal fibrillation, confinement dysfunction in chicken, sheering stress in sheep, and human-animal interaction stress in dogs; muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; hypertension; tachycardia; congestive heart failure; osteoporosis and premature birth in a mammal or bird, comprising administering to a subject in need of said treatment an amount of a compound according to claim 1, that is effective in treating such disorder or condition.

11. A method of treating a condition comprising administering a compound of claim 1 in an amount effective to treat said condition, wherein said condition is selected from the group consisting of:

- a) abnormal circadian rhythm;
- b) depression, further wherein a second compound for treating depression is administered, said second compound for treating depression having an onset of action that is delayed with respect to that of said CRF antagonist; and
- c) emesis.

12. The method of claim 11 wherein the condition is abnormal circadian rhythm, and the compound is combined with a second compound useful for treating a sleep disorder.

13. The method of claim 12, wherein said second compound is selected from the group consisting of tachykinin antagonists, agonists for GABA brain receptors, metalonergic compounds, GABA brain receptor agonists, 5HT₂ receptor antagonists, and D₄ receptor binding.

14. The method of claim 11 wherein said condition is depression, and wherein said second compound having delayed action for treating depression is selected from the group

consisting of selective serotonin reuptake inhibitors, tricyclic antidepressants, norepinephrine uptake inhibitors, lithium, bupropion, sertraline, fluoxetine, trazodone, and a tricyclic antidepressant selected from the group consisting of imipramine, amitriptyline, trimipramine, doxepin, desipramine, nortriptyline, protriptyline, amoxapine, clomipramine, maprotiline, and carbamazepine, and pharmaceutically acceptable salts and esters of the above-recited compounds.

15. The method claim 11 wherein said condition is emesis, further comprising administering a second compound for treating emesis.

16. The method of claim 15 wherein said second compound for treating emesis is selected from the group consisting of tachykinin antagonists, 5HT₃ antagonists, GABA agonists, and substance P inhibitors.

17. A pharmaceutical composition for treating a condition comprising a compound of claim 1 in an amount effective to treat said condition and a pharmaceutically acceptable carrier, wherein said condition is selected from the group consisting of:

- a) abnormal circadian rhythm;
- b) depression, further wherein a second compound for treating depression is administered, said second compound for treating depression having an onset of action that is delayed with respect to that of said compound of claim 1; and
- c) emesis.

18. A pharmaceutical composition according to claim 17, wherein the condition is abnormal circadian rhythm, and the compound is combined with a second compound useful for treating a sleep disorder.

19. A pharmaceutical composition according to claim 18, wherein said second compound is selected from the group consisting of tachykinin antagonists, agonists for GABA brain receptors, metalonergic compounds, GABA brain receptor agonists, 5HT₂ receptor antagonists, and D4 receptor binding .

20. A pharmaceutical composition according to claim 17 wherein said condition is depression, and wherein said second compound having delayed action for treating depression is selected from the group consisting of selective serotonin reuptake inhibitors, tricyclic antidepressants, norepinephrine uptake inhibitors, lithium, bupropion, sertraline, fluoxetine, trazodone, and a tricyclic antidepressant selected from the group consisting of imipramine, amitriptyline, trimipramine, doxepin, desipramine, nortriptyline, protriptyline, amoxapine, clomipramine, maprotiline, and carbamazepine, and pharmaceutically acceptable salts and esters of the above-recited compounds.

21. A pharmaceutical composition according to claim 17 wherein said condition is emesis, further comprising administering a second compound for treating emesis.

22. A pharmaceutical composition according to claim 21 wherein said second compound for treating emesis is selected from the group consisting of tachykinin antagonists, 5HT3 antagonists, GABA agonists, and substance P inhibitors.